AstraZeneca	AZD3355 (lesogaberan)
Mechanism of Action	γ-Aminobutyric acid (GABA) B receptor, 1 ($GABA_{B1}$) agonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=240 http://www.ncbi.nlm.nih.gov/gene/2550
Overview	AZD3355 is a potent, orally bioavailable $GABA_{B1}$ agonist. $GABA_B$ is a G protein-coupled receptor activated by the excitatory amino acid GABA that is expressed in both the CNS and periphery. Stimulation of $GABA_B$ receptors leads to the opening of potassium channels and is involved or implicated in a number of indications such as skeletal muscle spasm (where baclofen is indicated), pain, smoking cessation and gastric motility. AZD3355 is a potent, selective and reversible orally bioavailable $GABA_{B1}$ receptor agonist, with limited CNS access, that has been developed for the treatment of gastroesophageal reflux disease (GERD) as an add-on treatment to proton pump inhibitors to provide symptom relief in patients with a partial proton pump inhibitor (PPI) response. In preclinical studies, AZD3355 has an EC_{50} for increasing intracellular Ca^{2+} at the recombinant human $GABA_{B1}$ receptor of 8 nM and displaced GABA binding to rat brain membranes with an IC_{50} of 2 nM. In a panel of other targets, AZD3355 was only active at the $GABA_A$ receptor but with a 600-fold selectivity. AZD3355 reduced transient lower esophageal sphincter relaxations in the dog, producing approximately 50% inhibition at 3-7 µmol/kg.
Safety/Tolerability	A comprehensive safety assessment package has been performed on AZD3355 including pivotal reproductive toxicity studies and general toxicity studies of 3 month duration in mouse, 6 month duration in rat, and 12 month duration in dog. The only compound related toxicity seen in mice, rats, or dogs were changes in clinical signs, decreased body weight, and decreased food consumption. In rats, a dose-dependent diuretic effect was also noted. An effect on the liver was not apparent in preclinical species at any tested dose. AZD3355 has been administered to healthy volunteer subjects in single doses of up to 500 mg and in multiple ascending doses of up to 130mg for 7 days. Clinically relevant increases in liver enzymes have been reported in two Phase 2 studies, which returned to normal values after dosing was stopped.
Additional Information	AZD3355 has been studied in 4 Phase 2 clinical trials in GERD patients either alone or in combination with a PPI at doses of up to 240 mg BID for periods of up to 28 days. Although beneficial effects were seen in Phase 2b studies, these were not deemed to be sufficient for continuing development.
Suitable for and Exclusions	Reproductive toxicity studies support the inclusion of women of child-bearing potential in clinical studies provided that pregnancy is prevented using a reliable form of contraception. No data are available as yet to support use in pediatrics. Due to the emerging safety profile, proposals should be for diseases that require short term dosing regimens with appropriate liver monitoring and exclusion of patients or volunteers with liver abnormalities, or alternatively for diseases of severe unmet medical need where a case for tolerating potential adverse events can be made. Proposals for use in orphan indications would be particularly welcome, however, studies in GERD, ophthalmology or dermatology are not of interest.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=AZD3355
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=AZD3355%20or%20lesogaberan